

U.S.S.N. 09/834,700
BRAUN
ELECTION AND PRELIMINARY AMENDMENT

Please replace the paragraph on page 40, line 29 through page 41, line 22, with the following paragraph.

B2
Polymorphisms of the genome can lead to altered gene function, protein function or mRNA instability. AKAPs provide a mechanism for regulating ubiquitous cAMP-dependent kinase (PKA) activity by tethering PKA to specific subcellular locations thereby segregating it with particular components in a given signaling pathway and contributing to specificity in cellular responses to extracellular signals. AKAPs thus play a fundamental role in the basic functioning of cells, the response of cells to their environment and ultimately in the coordination of vital systems within an organism. Therefore, polymorphisms in AKAP gene sequences may significantly affect the proper functioning of cells and systems within organisms and could be directly linked with certain disorders or could predispose an organism to a variety of diseases and disorders, especially those involving alterations in cellular protein phosphorylation and/or signal transduction. Among such disorders and diseases are: neurodegenerative diseases, such as Alzheimer's Disease, cardiovascular disorders, cardiac disorders, particularly disorders associated with altered left ventricular function, cardiomyopathies, proliferative disorders, bipolar disorder and other neurological disorders, obesity, diabetes and certain peripheral retinopathies, such as retinitis pigmentosa. The discovery of AKAP gene polymorphisms, such as those described herein, provides for the identification and development of diagnostic and prognostic methods, also provided herein, and the development of drug therapies and treatment regimens. Furthermore, polymorphisms of AKAP genes aid in the study of AKAP protein structure and function, which also contributes to the development of diagnostic methods and therapies.

**U.S.S.N. 09/834,700
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ELECTION AND PRELIMINARY AMENDMENT**

Please replace the Table on page 43, lines 26-29 with the following Table.

B3

| Name | GenBank Accession No. | SNP | Location |
|------|-----------------------|-----|----------|
| 10-1 | AC005730 | T/C | 156277 |
| 10-6 | AC005730 | C/G | 83587 |
| 10-7 | AC005730 | G/A | 129600 |

Please replace the paragraph on page 69, lines 14-25, with the following paragraph.

B4

An example of possible candidate morbidity susceptibility genes are mutants of the A kinase anchoring protein (AKAP) genes. Protein phosphorylation is an important mechanism for enzyme regulation and signal transduction in eukaryotic cells. cAMP dependent protein kinase (PKA) mediates a variety of hormonal and neurotransmitter responses by phosphorylating a wide variety of substrates including enzymes, membrane receptors, ion channels and transcription factors. AKAPs direct the subcellular localization of cAMP-dependent protein kinase by binding to its regulatory subunits and therefore plays a role in G-protein mediated receptor-signalling pathways. (Huang et al. Proc. Natl. Acad. Sci., USA 94:11184, 1997). AKAPs have a PKA binding region located in their COOH-terminal portion.

Please replace the paragraph on page 91, line 23 through page 92, line 21, with the following paragraph.

B5

Ribozymes may be prepared by chemical synthesis or produced by recombinant vectors according to methods established for the synthesis of RNA molecules. See, e.g., Sambrook et al., Molecular Cloning, A Laboratory Manual, 2d ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1989), incorporated herein by reference. The ribozyme sequence may be synthesized, for example, using RNA polymerases such as T7 or SP6. The ribozymes may be prepared from a corresponding DNA sequence (DNA which on transcription

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yields a ribozyme) operably linked to an RNA polymerase promoter such as the promoter for T7 RNA polymerase or SP6 RNA polymerase. A DNA sequence corresponding to a ribozyme may be ligated in to a DNA vector, such as a plasmid, bacteriophage or other virus. Where the transfer vector contains an RNA polymerase promoter operably linked to DNA corresponding to a ribozyme, the ribozyme may be conveniently produced upon incubation with an RNA polymerase. Ribozymes may therefore be produced in vitro by incubation of RNA polymerase with an RNA polymerase promoter operably linked to DNA corresponding to a ribozyme, in the presence of ribonucleotides. In vivo, prokaryotic or eukaryotic cells (including mammalian cells) may be transfected with an appropriate vector containing genetic material corresponding to a ribozyme, operably linked to an RNA polymerase promoter such that the ribozyme is transcribed in the host cell. Ribozymes may be directly transcribed in vivo from a transfer vector, or alternatively, may be transcribed as part of a larger RNA molecule. For example, DNA corresponding to ribozyme sequence may be ligated into the 3' end of a carrier gene, for example, after a translation stop signal. Larger RNA molecules may help to stabilize the ribozyme molecules against nuclease digestion within the cells. On translation the carrier gene may give rise to a protein, whose presence can be directly assayed if desired, for example, by enzymatic reaction when the carrier gene encodes an enzyme.

Please replace the paragraph on page 94, lines 8-31, with the following paragraph.

BC

The following examples are included for illustrative purposes only and are not intended to limit the scope of the invention. The practice of methods and development of the products provided herein employ, unless otherwise indicated, conventional techniques of cell biology, cell culture, molecular biology, transgenic biology, microbiology, recombinant DNA, and immunology, which are within the skill of the art. Such techniques are explained fully in the literature. See, for example, Molecular Cloning A Laboratory Manual, 2nd Ed., ed. by Sambrook, Fritsch and Maniatis (Cold Spring Harbor Laboratory Press: